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# Norfloxacin as a model hydrophobic drug with unique release from liquisolid formulations prepared with PEG200 and Synperonic PE/L-61 non-volatile liquid vehicles



Ammar Said Suliman, Rosaleen J. Anderson, Amal Ali Elkordy \*

Department of Pharmacy Health and Well-being, University of Sunderland, UK

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## ABSTRACT

The purpose of the study is to investigate dissolution behaviour of norfloxacin as a model hydrophobic drug through application of liquisolid technology. Norfloxacin was prepared as liquisolid formulations using either flowability or compressibility liquisolid tests. The dissolution profiles were evaluated and compared to counterpart conventional norfloxacin tablets. Two non-volatile liquid vehicles were used in the preparation of norfloxacin liquisolid formulations; Poly Ethylene Glycol (PEG200) and Synperonic PE/L-61. The liquisolid formulations of norfloxacin were tested according to the specification of British Pharmacopoeia (BP) quality control tests. Moreover, the pre-preparation evaluation tests, such as powder flowability Carr index, differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR), were applied for further investigation of the physicochemical properties of the liquisolid formulations. The results indicated that the percentage of norfloxacin release in acetate buffer solution (pH = 4.0) is higher than in distilled water. Also, at the first 20 min, the percentage of the drug release is higher only in the decreased amount of liquid vehicle formulations compared with the conventional tablet. Generally, the conventional tablet dissolution profile is either similar or higher than liquisolid tablets. Moreover, Synperonic PE/L-61 liquisolid tablets showed higher dissolution profiles than PEG200 liquisolid tablets, although the solubility of norfloxacin in PEG200 (2.507 mg/ml) is much higher than in Synperonic PE/L-61 (0.167 mg/ml). In conclusion, increasing the percentage of liquid vehicle in the prepared norfloxacin liquisolid formulations does not necessarily lead to increase in the percentage of the drug release in distilled water dissolution medium.

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## 1. Introduction

Oral delivery administration can be considered as a frequently employed route among drug delivery systems. This is due to its cost effectiveness, least sterility restrictions during manufacturing, ease of administration and flexibility of formulation design. Consequently, several pharmaceutical companies select bioequivalence oral drug production preferably [1].

Oral compacts, containing poor water soluble drugs, usually involve high doses in order to increase therapeutic plasma concentration level after oral administration. Low level of solubility does not help to attain therapeutic levels. Thus, it is considered as a major problem facing any formulation design for both new chemical entities and generic development [2].

According to bio-pharmaceutics classification system (BCS), more than 40% of drugs are poorly water soluble drugs. These drugs have slow absorption toward plasma, leading to not only low and inadequate

bioavailability, but also raise the toxicity in gastrointestinal mucosa due to its accumulation in GI track. As a result, the improvement of drug solubility and dissolution is one of the major goals to enhance oral bioavailability [3].

Recent new synthesized drugs show an increase in the number of hydrophobic groups, which have difficulties in oral delivery due to their poor solubility and bioavailability. An example of these drugs is norfloxacin. It is used to treat urinary tract infections because it works as a chemotherapeutic antibacterial agent. Only 30–40% of norfloxacin can be absorbed through passive diffusion [4]. Moreover, in vitro tests, using either non-everted intestinal sacs or caco-2 cells, recorded low permeability percentage, confirming norfloxacin classification as a poorly permeable compound [5].

In addition to this, norfloxacin can be classified as a zwitterionic molecule. It represents a U-shaped profile in terms of pH-solubility studies—a high solubility when pH is less than 5, low solubility in neutrality region, and a high again when pH is over 10. As a result, it is classified as a low water soluble drug [6].

One method used to enhance both solubility and dissolution of hydrophobic drugs is liquisolid pharmaceutical technique. The definition of liquisolid systems is “they are compacts with acceptable flowing

\* Corresponding author at: University of Sunderland, Department of Pharmacy, Health and Well-being, Sunderland SR1 3SD, UK. Tel.: +44 1915152576; fax: +44 1915153405. E-mail address: [amal.elkordy@sunderland.ac.uk](mailto:amal.elkordy@sunderland.ac.uk) (A.A. Elkordy).

and compressible powdered forms of liquid medications, which represent oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable non-volatile solvent systems termed the liquid vehicles" [7]. According to this definition, liquisolid method can be selected to improve the water solubility of norfloxacin.

A range of several surfactants has been selected, in this study, for liquisolid preparations. The selection stands on covering a wide range of Hydrophobic Lipophilic Balance (HLB) values. For example, poly ethylene glycol 200 (PEG 200), which has HLB value = 18.1 and poloxamer 181 copolymer (Synperonic PE/L-61) with HLB = 3.

Regarding PEG200, it is a stable-hydrophilic water-miscible surfactant. It can be used as a suspending agent to form liquid medication with a hydrophobic drug that allows miscibility in water. A wider view to poly ethylene glycol surfactants determines an advantage for the low molecular weight group, which increases the rate of the drug release from liquid medication. On the other hand, the higher molecular weight, more enhancement of the effectiveness of compact binder, even though when the concentration is over 5%, could prolong the disintegration. In general, PEGs are stable in both air and solution. However, the low grades of PEG demonstrate a level of hygroscopicity. In conclusion, PEGs can be considered as a good solvent to prepare immediate release liquisolid formulations [8].

Another example is Poloxamer 181, which represents the group of low HBL value liquid vehicles. The chemical structure consists of three synthetic blocks, representing hydrophilic and lipophilic parts. The first and the third blocks are two poly (oxyethylene) groups from each side, while the middle block is thirty poly (oxypropylene) groups. This structure allows the surfactant to be more hydrophobic with HLB value = 3. The general use of poloxamers is as binders or coaters in tablet production. However, the physical properties and viscosity of these surfactants change depending on the length chain of hydrophobic and hydrophilic blocks. Also, poloxamers are stable if they present in acids, alkaline or metal ions. They are classified as non-toxic and non-irritant substances. As a result, the physicochemical properties make them good candidates to be used in liquisolid formulations [8].

The concept of liquisolid system stands on two fundamental terms; the flowable  $\emptyset$  value and compressible  $\psi$  number liquid retention potentials. The  $\emptyset$  value defines an acceptable level of powder flowability when adding the maximum amount of a given non-volatile liquid, whereas the  $\psi$  number specifies an acceptable level of powder compressibility when adding the maximum amount of the non-volatile liquid. Spireas et al. indicated two methods to predict the two terms. The  $\psi$  number and  $\emptyset$  values are determined by applying liquisolid compressibility (LSC) test and liquisolid flowability (LSF) test, respectively [7].

Regarding the LSF test, several powder systems are prepared to contain different values of excipient ratio (R) where  $R = Q/q$ ; Q represents the weight of a carrier excipient and q represents the weight of a coating excipient. Each mixture will contain an increased amount of non-volatile liquid which will be used in liquisolid preparation. The flowability of each prepared mixture will be assessed by flow metre, angle of slid, angle of repose or any suitable flowability test to specify the flowable liquid load factor  $\emptyset_{L_f}$  of each powder system. The  $\emptyset_{L_f}$  can be given by the following equation

$$\emptyset_{L_f} = W/Q, \text{ where } W \text{ is the weight of the liquid vehicle and } Q \text{ is the weight of the carrier material.}$$

Finally,  $\emptyset$  value of a powder (carrier or coating excipients) will be determined by plotting  $\emptyset_{L_f}$  against reciprocal excipient ratio (1/R) where the slope represents  $\emptyset$  value of the carrier and the intercept indicates the  $\emptyset$  value of the coating.

In liquisolid compressibility (LSC) test, the same liquid/powder admixture prepared in the previous test will be used to assess the maximum crushing strength of the compacts that can be obtained by

applying a plateau compression forces. The average of crushing strength of each admixture will be divided on the average of the weight of the compacted tablets in order to determine the pacticity  $\Omega$  value. The determination of the net liquid/solid weight composition ( $C_w$ ) of the crushed tablets will be used to indicate the intrinsic pacticity ( $\Omega_o$ ) and sponge index ( $\sigma_i$ ) by plotting  $\log \Omega$  versus  $C_w$  to give a log-linear equation:  $\log \Omega = \log \Omega_o - \sigma_i * C_w$ .

The compressible liquid retention potential of the powder system ( $\psi_{mix}$ ) can be given by the following equation  $\psi_{mix} = (\log \Omega_o - \log 20) / \sigma_i$ , where the fixed value of the logarithm twenty comes from applying the plateau force pressures to achieve the maximum crushing strength which gives a pacticity  $\Omega = 20$  kg/g.

Finally, the compressible liquid load factor ( $\psi_{L_f}$ ) of the powder system can be determined from the following equation:  $\psi_{L_f} = \psi_{mix} (1 + 1/R)$ . By plotting the  $\psi_{L_f}$  for each admixture against the reciprocal excipient ratio (1/R) will give a linear equation with a slope equals to compressible liquid-retention potential ( $\psi$  number) of the carrier and the intercept is the compressible liquid-retention potential ( $\psi$  number) of the coating.

The optimum load factor ( $Lo$ ), which will be used to determine the optimum quantities of the carrier and coating excipients, will indicate the acceptable flowing and compressible liquisolid system. This term is given as follows;

$$Lo = \emptyset_{L_f} \text{ when } \emptyset_{L_f} < \psi_{L_f}$$

or

$$Lo = \psi_{L_f} \text{ when } \emptyset_{L_f} > \psi_{L_f}$$

where  $\emptyset_{L_f} = \emptyset_{ca} + \emptyset_{co} * (1/R)$  and  $\psi_{L_f} = \psi_{ca} + \psi_{co} * (1/R)$ .

The optimum quantity of the carrier  $Q_o$  is given from this equation:  $Q_o = W/Lo$ ; where  $W$  = weight of drug/weight of non-volatile liquid.

Finally, the optimum quantity of the coating material  $q_o$  is given as follows:  $q_o = Q_o/R$ . All the mathematical calculation is mentioned in this article [7].

## 2. Materials and methods

### 2.1. Materials

Norfloxacin was obtained from Sigma-Aldrich, Co., UK. Other powder excipients used to prepare the tablets include microcrystalline cellulose (AvicelPH101), (FMC Biopolymer Corp., Philadelphia, USA); colloidal silicon dioxide (Cab-O-Sil® M-5 DP, particle size: 0.2–0.3  $\mu$ m), (Cabot GmbH, Werk Rheinfelden, Germany); croscarmellose sodium USP/NF/EP (Vivasol®), (CHP Carbohydrate Pirna GmbH & Co. KG, Pirna, Germany); magnesium stearate (MEDEX, Morthants).

The surfactants used in screening solubility tests are Propylene Glycol (Sigma-Aldrich, Germany); Sorbitan Monooleate (Span 80) (Sigma-Aldrich, Germany); Polyethylene Glycol 200 (Sigma-Aldrich, USA); Sorbitan Monolaurate (Span 20) (Sigma-Aldrich, South Korea); Synperonic PE/L61 (ICI surfactants, Everberg, Belgium); Polyethylene Glycol 400 (Sigma-Aldrich, Belgium); Cremophore EL (poly-oxy-35-castor oil) (BASF, Germany); pluronic®L-35 (Sigma-Aldrich, USA); Polyethylene Glycol 300 (Sigma-Aldrich, Germany); Tween 80 viscous liquid (Sigma-Aldrich, UK); Tween 20 viscous liquid (sigma-Aldrich, France).

Acetic acid (Sigma-Aldrich, UK) with Sodium Hydroxide pellets (Sigma-Aldrich, UK) were used for acetate buffer solution (pH = 4.0) preparation. Orthophosphoric acid HPLC electrochemical grade (Fisher Scientific, UK) with Acetonitrile HPLC grade (Fisher Scientific, UK) were used together in drug content uniformity test.

Finally, buffer tablets pH = 4.0 (BDH Chemical Ltd., England) and Buffer tablets pH = 7.0 (Asons Laboratory reagent, UK) are used for

calibrating Jenway 3505 pH metre. All materials were of pharmacological or analytical grade.

## 2.2. Pre-formulation studies

### 2.2.1. Solubility studies

The solubility of norfloxacin in several surfactants, which are PEG200, PEG300, PEG400, Span 20, Span 80, Tween 20, Tween 80, Synperonic PE/L61, Pluronic L-35, Propylene Glycol and Cremophore EL as well as distilled water, was performed to evaluate the drug solubility of the non-volatile liquid vehicles as solvent and suspending agents for norfloxacin. Saturated solutions were prepared by adding excess amount of norfloxacin into 1 ml of each liquid vehicle. The resulting solutions were sealed and kept at room temperature ( $24 \pm 1^\circ\text{C}$ ) for 72 h. After this period, the solutions were centrifuged using a centrifuge rotor (Mikro 12–24, Hettich, Germany) for 10 min, at 4000 U/min. The supernatants were transferred to 1 ml eppendorf tubes and re-centrifuged until no drug particles precipitate. The drug concentration in each supernatant was determined using a single beam UV/Vis spectrophotometer (Model M501, Camspec LTD, Cambridge, UK) at 318 nm after dilution in acetonitrile as appropriate. The concentration of norfloxacin in each liquid vehicle was calculated based on the calibration curve of norfloxacin.

### 2.2.2. Determination of optimal flowable liquid-retention potential ( $\phi$ -value)

The angle of slide measurement (Figs. 1 and 2) was used to determine the optimal flowable liquid-retention potential ( $\phi$ -value) of each powder excipient (Avicel® PH101 and Cab-o-Sil® M-5 DP) with Synperonic® PE/L61 and PEG200. Each powder excipients (2.5 g) was mixed with increasing amounts of the two non-volatile liquid vehicles, and the resulting admixture was placed on an edge of a polished metal plate, tilted gradually until the admixture starts to slide. The angle of the plate with the horizontal surface is defined as the angle of slide. The  $\phi$ -value of Avicel® PH101 and Cab-o-sil® M-5 DP in different concentrations of liquid vehicles was calculated based on the following equation:

$$\phi\text{-value} = \text{weight of the liquid vehicle} / \text{weight of solid}.$$

The calculated  $\phi$ -values against the resulting angle of slides were plotted to select the optimum  $\phi$ -value of the powder excipient in the corresponding liquid vehicle at  $33^\circ$ . However, all corresponding angles were less than  $33^\circ$ , so the nearly highest angle was selected to represent the optimum flowability number [11].

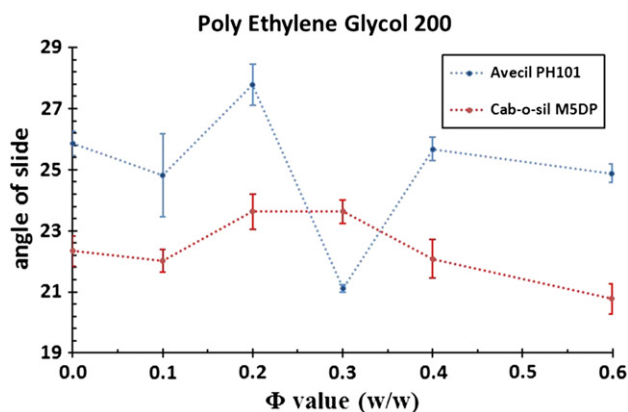


Fig. 1. The optimum flowability value for PEG200 and Avicel PH101 admixture (0.2) and PEG200 with Cab-o-sil M5DP admixture (0.2).

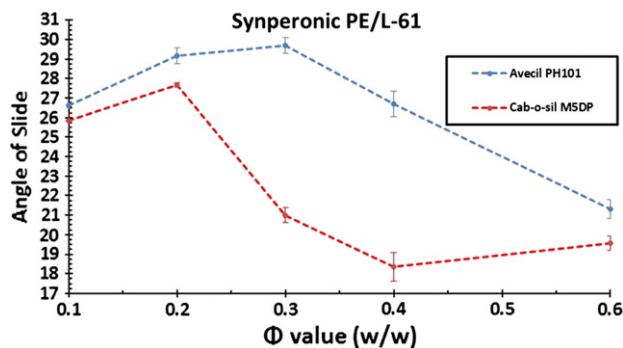


Fig. 2. The optimum flowability value for Synperonic PE/L-61 and Avicel PH101 admixture (0.3) and Synperonic PE/L-61 with Cab-o-sil M5DP admixture (0.2).

### 2.2.3. Determination of compressibility liquid-retention potential ( $L_f^\Psi$ )

Powder systems consisting of Avicel PH101 and Cab-o-sil M5DP at different excipient ratios;  $R = 10$  and  $R = 20$ ; where  $R$  equals to the weight of Avicel PH101 divided by weight of Cab-o-sil M5 DP were prepared with increasing amount of Synperonic® PE/L61. Firstly, the mixtures without the liquid vehicle were compressed by Manesty Type 3 single punch compactor at a specific weight and a compression force to give the maximum tablet hardness, which are measured by Schleuniger-2E hardness tester. Then, the liquid vehicle was added gradually to give different liquid/solid weight compositions ( $C_w$ ). The pacticity ( $\Omega$ ) of each admixture is calculated by dividing the average hardness of tablets on the average weight of the crushed tablets. By determining the average liquid content of the crushed compacts and calculating the net liquid/solid weight composition ( $C_w$ ) of the crushed liquid/powder admixture, a plot of  $C_w$  against log-pacticity to determine the characteristic intrinsic pacticity ( $\Omega_o$ ) as an index ( $\sigma_0$ ) of the powder system, where

$$\log \Omega = \log \Omega_o - \sigma_0 * C_w.$$

The compressible liquid retention potential ( $\Psi$ -number) of the powder system ( $\Psi_{\text{mix}}$ ) was calculated according to the following equation:

$$\Psi_{\text{mix}} = \frac{\log \Omega_o - \log 20}{\sigma_0}.$$

Finally, by calculating the  $\Psi_{\text{mix}}$  value for each powder system, the compressible liquid-load factor ( $L_f^\Psi$ ) of the mixture of Synperonic® PE/L61 with powder excipient (Avicel PH101 and Cab-o-sil M5DP) at specific excipient ratios ( $R$ ) was determined according to the following equation:

$$L_f^\Psi = \Psi_{\text{mix}} \left( 1 + \frac{1}{R} \right).$$

This method was applied simulating Liquisolid Compressibility (LSC) Test [7].

## 2.3. Liquisolid formulations and compact preparations

The calculated amounts of both carrier and coating materials in each liquisolid formulations were determined according to the flowability numbers for the formulations containing PEG200 and compressibility liquid load factor for the Synperonic PE/L-61 formulations. The reason for choosing the compressibility liquid load factor in these formulations is the lower value obtained compared with flowability liquid load factor for the same formulations. However, this is not applied for PEG200 formulations due to the ability to compact the powder at flowability liquid load factor and obtain acceptable compacts, which means it is



less than the corresponding compressibility liquid load factor for the same formulations [7].

The equation used to calculate the flowability liquid load factor is:  $L_f^\phi = \phi_{car} + \phi_{co} \left(\frac{1}{R}\right)$ , where  $\phi_{car}$  and  $\phi_{co}$  is the flowability number of the carrier and coating respectively, which are determined from the highest angle of slide under 33°.

The excipient ratio (R) was chosen to be either 10 or 20 for all liquisolid formulations. Moreover, 20 mg of norfloxacin active ingredient was selected to be in each tablet. As a result, the required amount of liquid medication (W) is calculated depending on drug concentration in the liquid medication (i.e. 20%w/w or 40%w/w). After determining the liquid load factor, the desired amount of carrier can be calculated by applying the following equation:  $L_f = \frac{W}{Q}$  and the specific amount of coating is form  $R = Q/q$ . The liquisolid and conventional formulations are summarised in Table 1.

The detailed procedure for liquisolid formulation preparation is as follows; firstly, pure norfloxacin was dispersed in the liquid vehicle (PEG200 or Synperonic® PE/L61) to form a liquid medication. Then, the carrier (Avicel PH101) and the coating (Cab-o-sil M5DP) excipients were added to the liquid medication with continuous mixing by mortar and pestle until obtaining a dry powder mixture.

Carmellose sodium disintegrant (5% w/w of the unit dose) and magnesium stearate lubricant (1% w/w of the unit dose) were added to the liquisolid mixture with continuous mixing until reach to a homogeneous mixture.

Finally, all formulations were compacted into tablets using the single punch tablet press with acceptable level of hardness. For high unit dose weight, each sample unit was divided into 2 or 4 tablets so that they contain 20 mg of norfloxacin. The reason for this is to ensure that each tablet is within a reasonable size and hardness.

By using mortar and pestle, the conventional norfloxacin tablets were prepared by mixing carrier and coating ( $R = 20$ ) with 20 mg of the drug and with the same percentage of lubricant and disintegrant. The resulting powder mixture was directly compressed into tablets through the single punch compactor.

## 2.4. Pre-compression studies

### 2.4.1. Determination of flow property

Assessing the flowability of prepared liquisolid powders depends on Carr's Compressibility Index (CI). It is calculated from determination of the relative poured bulk density ( $P_b$ ) and the tapped density ( $P_t$ ) of each liquisolid powder formulation. The weight of each liquisolid powder formulation was recorded and then the powder was poured into a 250 ml cylinder on a tap volumeter (JV1000, Copley Scientific, UK). Both poured bulk volume ( $V_b$ ) and tapped volume ( $V_t$ ), which is the constant volume obtained after application of a sufficient number of taps (usually after 500 taps  $\times$  3 times), are recorded. The densities are determined from dividing

each weight of the liquisolid powder on the relative volume. Finally, %CI is calculated by applying the following equation [9]

$$\%CI = 100 \times (P_t - P_b) / P_t.$$

### 2.4.2. Differential scanning calorimetry (DSC)

Pure norfloxacin and all liquisolid and conventional powders were exposed to DSC scan via DSC Refrigerated Cooling System (Model Q1000, TA Instruments, UK). Each sample contained about 3–6 mg. Then, it was hermitically sealed in an aluminium pan before analysis. Two samples of indium (10 and 12 mg) were used to validate the accuracy of the instrument. The investigation of the thermal behaviour of each sample was at a scanning rate 10 °C/min, from 0 °C to 300 °C.

### 2.4.3. Fourier transform infrared spectroscopy (FTIR)

Infrared spectra were acquired for norfloxacin, Synperonic® PE/L61, PEG200, Avicel® PH101, Cab-o-sil® M-5 DP, Vivasol®, magnesium stearate and all liquisolid and conventional formulations using Spectrum BX FTIR Spectrophotometer (Perkin–Elmer, Cambridge, UK). Small amount of each sample was directly loaded into the instrument without any treatments. The frequency ranged from 2000  $\text{cm}^{-1}$  to 600  $\text{cm}^{-1}$  at 1.0  $\text{cm}^{-1}$  resolution. The data was obtained by Spectrum BX series software version 5.3.1 and transferred to Microsoft Excel®.

## 2.5. Evaluation of norfloxacin liquisolid tablets

### 2.5.1. Drug content uniformity, tablet dimensions, hardness, tensile strength, friability and disintegration tests

For content uniformity test, tablets containing 20 mg of norfloxacin were weighed and crushed by mortar and pestle in order to determine the drug content in liquisolid and conventional tablets. Then, the crushed powder was dissolved in a suitable solvent; acetate buffer solution at pH = 4 for tablets containing Synperonic PE/L-61 and a prepared mixture of acetonitrile with orthophosphate buffer pH = 4 (150 ml: 750 ml). The result solutions were mixed for 1 h and filtered. Finally, the samples were analysed for determining the drug concentration using UV spectrophotometer at 315 nm. The percentage of drug content with respect to the theoretical amount was determined.

Tablets friability was measured using a Comply FRV 1000 friability tester and disintegration times were determined employing Coply DTG200 disintegration tester at 37 °C in distilled water. Tablet thickness and diameter were determined by micrometre (Moor and Wright, England). Tensile strengths of tablets were calculated by applying the following equation:

$$S = \frac{2P}{\pi} \times d \times t$$

**Table 1**

The percentage of liquisolid and conventional tablet formulations.

Formula	Non-volatile liquid vehicle	Drug conc. in liquid vehicle (%w/w)	R value	Liquid vehicle mg	Drug mg	Carrier mg	Coating mg	Liquid load factor $L_f$	Disintegrant mg (~5%)	Lubricant mg (~1%)	Unit dose mg
1	PEG 200	20	10	80	20	454.55	45.45	0.22	31.91	6.38	638.30
2	PEG 200	20	20	80	20	476.19	23.81	0.21	31.91	6.38	638.30
3	PEG 200	40	10	30	20	227.27	22.73	0.22	15.96	3.19	319.15
4	PEG 200	40	20	30	20	238.10	11.90	0.21	15.96	3.19	319.15
5	S-L-61 <sup>a</sup>	20	10	80	20	716.93	71.69	0.14	47.27	9.45	945.35
6	S-L-61	20	20	80	20	962.64	48.13	0.10	59.08	11.82	1181.68
7	S-L-61	40	10	30	20	358.47	35.85	0.14	23.63	4.73	472.67
8	S-L-61	40	20	30	20	481.32	24.07	0.10	29.54	5.91	590.84
Conventional	–	–	–	–	20	254.45	25.50	–	16.00	3.20	319.15

<sup>a</sup> S-L-61: Synperonic PE/L-61.

where  $S$  is the tensile strength,  $P$  is the crushing force which determined by Schleniger-2E hardness tester,  $d$  is the diameter of the tablet and  $t$  is the tablet thickness.

### 2.5.2. In vitro dissolution studies

In vitro dissolution studies were performed for pure norfloxacin, conventional and all liquisolid tablet formulations by using USP dissolution apparatus II (Caleva 8ST Ltd., Dorset, UK). Two different dissolution media were used for all liquisolid and conventional tablets; distilled water ( $pH = 6.1$ ) and the acetate buffer solution ( $pH = 4.0$ ). Both medium volumes were 750 ml with a paddle speed 50 rpm maintained at  $37^\circ\text{C}$  according to BP specifications [9]. 10 ml sample was withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 45, 60 and 90 min, and the withdrawn samples were replaced with equal volumes of the dissolution medium. The drug content in each withdrawn sample was determined using UV/Vis spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK) at 315 nm for acetate buffer medium and 321 nm for distilled water medium. The reported data are an average of three samples with the relevant standard deviation and the calibration curve was used to calculate the relative drug concentration. Each sample included a number of tablets (i.e. one, two or four tablets) so that it contains 20 mg of the active ingredient. This idea was taken from a similar study [12]. The similarity factor ( $f_2$ ) was used as a statistical technique to compare between the dissolution profiles.

$f_2 = 50 \times \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$ , where  $R_i$  is the reference data,  $T_i$  is the test data,  $n$  is the number of samples. If the percentage is over 50%, this means that the two groups of data are similar; otherwise it is not significantly similar.

### 2.5.3. Kinetic model analysis of drug release

In order to inspect the mechanism of norfloxacin release from liquisolid and conventional tablets, several kinetic release models were applied on data obtained from dissolution tests. These models are; zero order, first order, and Higuchi and Hixson–Crowell kinetic models. Regarding zero order model, it can be described as a system that all drug particles transfer process to dissolution medium that is confined to the surface area of the system. The data of the cumulative percentage of the drug release can be plotted against the time [13]. In terms of first order, the drug release is related to the drug concentration and it can be applied by plotting logarithm of the percentage release of the remaining drug versus the time [13]. Moreover, in Higuchi model, plotting the cumulative percentage of the drug release against the square root of time should be linear if the drug release from the tablet a controlled diffusion [14]. Furthermore, Hixson–Crowell model depends on the theory that particle area is proportional to the cubic root of its volume. As a result, the plotting data is the cubic root of the drug remaining in the tablet versus the time [15]. The highest square of correlation coefficient ( $R^2$  value) was selected to indicate the most appropriate model to represent the norfloxacin release from liquisolid formulation [13]. Statistically, Paired  $t$ -tests were used to determine whether there is a significant difference between the models, regardless of the differences in the type of formulations. Due to dealing with model predictions, the significant probability was selected to be more robust at 0.1 levels.

### 2.6. Statistical analysis

In the tests of evaluation norfloxacin tablet test (flowability, friability, hardness, tensile strength, content uniformity and disintegration tests), Paired  $t$ -test was used to compare between the PEG200 liquisolid tablets and Synperonic PE/L-61 liquisolid tablets, whereas One sample  $t$ -test was used to compare between liquisolid tablets in general, PEG200 liquisolid tablets and Synperonic PE/L-61 liquisolid tablets in one side and conventional tablet from the another side. All the data results were quoted as significant where  $P < 0.05$ .

## 3. Results and discussions

### 3.1. Solubility studies

From Table 2, norfloxacin has the highest solubility value in PEG200, whereas the lowest one is in Synperonic PE/L-61. It can be noticed that with the increase in the molecular weight of the PEGs, the solubility of norfloxacin decreases. Moreover, the drug has low solubilities with both types of poloxamers (Synperonic PE/L-61 and Pluronic L-35), although they have different HLB values, i.e. Pluronic L-35 is  $>20$  and Synperonic PE/L-61 equals to 3. The solubility of the drug in distilled water is 0.34 mg/ml, allowing the drug to be classified as a very slightly soluble one. The highest and the lowest solubility values were chosen to be used in the liquisolid formulations to investigate the effect of the solubility on the percentage of the drug release in the dissolution tests.

### 3.2. Pre-compression studies (characterization of powder admixtures)

#### 3.2.1. Determination of flow property

The importance of powder flowability in tablet production comes from its effect on the consistency of tablet weight and drug content. One of the methods to determine the powder flowability is Carr's compressibility index, where the percentage of the differences between bulk powder density before and after tapping divides on the bulk density. This law was used to determine the flowability of all liquisolid and conventional formulations. The results are summarised in Table 3, and the criteria depend on British Pharmacopoeia, indicating that any formulation that has CI% below 25 represents better flow properties [9]. The statistical analysis shows that there is a significant differences between liquisolid formulations and conventional powder ( $P = 0.002 < 0.05$ ). These differences come mainly from the difference between the Synperonic PE/L-61 formulations and conventional powder ( $P = 0.047 < 0.05$ ). In general, all liquisolid formulations recorded CI percentages over 20% and no significant differences between PEG200 liquisolid formulations and Synperonic PE/L-61 liquisolid formulations ( $P = 0.406 > 0.05$ ).

According to Spireas et al., the amount of carrier and coating materials in the liquisolid formulations determines the flowability as they play an important role in adsorbing the liquid vehicle on the surface of the carrier, allowing coating particles specifying a certain amount of retained liquid vehicle with an acceptable level of flowability [16]. Consequently, the increasing amount of the liquid in the formulation leads to increase the carrier and coating particles which enhance the powder flowability and reduce the %CI. This clearly appears in both PEG200 and Synperonic PE/L-61 liquisolid formulations, wherever there is a high percentage of the liquid, there is an increase in the amount of carrier and coating. However, the low percentage of the liquid vehicle leads to less amount of carrier and coating materials and produces either poorly or very poorly flowable formulations.

#### 3.2.2. Differential scanning calorimetry (DSC)

Figs. 3 and 4 represent a comparison between all thermograms of the liquisolid and conventional formulations with and without the thermogram of pure norfloxacin. It is clear that norfloxacin pure drug has a sharp endothermic peak at melting temperature ( $222.36^\circ\text{C}$ ) with relatively high enthalpy value (107.7 J/g). This sharp peak indicates the crystallinity of the drug and the melting of the sample, referring the end of the thermogram to the decomposition of norfloxacin [17]. Moreover, the sharp endothermic peak disappears in all liquisolid formulations (PEG200 and Synperonic PE/L-61), indicating a change in the crystallinity nature of the drug.

Furthermore, the percentage of R value seems to have no main effects on the liquisolid thermograms. This is contrary with the type and the percentage of the liquid vehicles. In the case of PEG200 liquisolid formulations, a broader peak appears when the percentage of the weight of norfloxacin to the weight of PEG200 is 40%w/w at  $139.04^\circ\text{C}$  with a small amount of enthalpy capacity equals to 27.92 J/g. Although this

indicates that the drug is not completely dissolved or dispersed in PEG200, the reduction in melting temperature point improves that there is a certain of reaction happened between the vehicle and the drug. Complementarily with this, the broad small peak disappeared completely when increasing the amount of PEG200 vehicle in the liquisolid formulations.

Guyot et al. reached to the same conclusion in terms of disappearance of the endothermic norfloxacin peak at 222 °C. However, due to using another type of liquid vehicle (PEG6000) and changing the pharmaceutical preparation to solid dispersion technique, another peak appeared at 62 °C when the percentage of the surfactant exceeds 50% with the drug [17]. On the other hand, very tiny peaks were indicated at the same melting temperature of norfloxacin with very small enthalpy capacities, which ranged from 0.08 J/g at 20%w/w norfloxacin/Synperonic PE/L-61 to 0.61 J/g at 40%w/w norfloxacin/Synperonic PE/L-61. This is accompanied with one or two temperature decrease (220–221 °C). The probable reason for this is the less degree of solubility of norfloxacin in the vehicle (0.167 mg/ml). However, this does not give a negative effect on the dissolution profile. On contrary, it enhances the percentage of the drug release compared with PEG200 liquisolid formulations as whole.

Finally, the sharp endothermic peak appears clearly in the case of the conventional powder, where there is no added liquid vehicle to the formulations. It appears at 221.37 °C with enthalpy equals to 0.9524 J/g, indicating a slightly change in drug crystallinity compared with the liquisolid formulations.

### 3.2.3. Fourier transform infra-red spectroscopy (FTIR)

Figures from 5 to 10 provide information about IR spectra of pure norfloxacin (Fig. 5), the carrier and the coating (Fig. 6), lubricant and disintegrate (Fig. 7), the liquid vehicles (Fig. 8), the PEG200 liquisolid formulations (Fig. 9) and the Synperonic PE/L-61 liquisolid formulations (Fig. 10). The last two figures provide a comparison between the liquisolid formulation, conventional powder and pure norfloxacin powder.

From Figs. 9 and 10, it is obvious that characteristic fingerprint FTIR peaks of norfloxacin between 1700  $\text{cm}^{-1}$  and 1250  $\text{cm}^{-1}$  faced massive changes in the IR spectra related to liquisolid formulations. These changes are expressed in several ways, such as reduced in the intensity of signal, shift or disappearance of the whole peaks, suggesting that there is interaction between the drug and the excipients.

In addition to this, the decreased percentage of the transmittance between 1190  $\text{cm}^{-1}$  and 1000  $\text{cm}^{-1}$  wavenumbers in liquisolid formulations suggests a particular interaction between norfloxacin with the liquid vehicles. For example, there is a simultaneous increase of the absorptive intensity of these IR spectra when increasing the percentage of PEG200 in the liquisolid formulations. The intensive peak from this increase in the liquid concentration cannot be seen as

**Table 2**

The solubility of norfloxacin in a range of surfactants and distilled water at room temperature (24 °C).

Liquid vehicle	Average of solubility (mg/ml)	Standard deviation
PEG200	2.507	0.066
Span 80	1.997	0.266
PG	1.734	0.239
PEG300	1.547	0.132
Tween 20	1.085	0.056
Tween 80	0.954	0.251
Span 20	0.6374	0.033
PEG400	0.428	0.131
Cremophore EL	0.366	0.113
Pluronic L-35	0.35	0.194
Distilled water	0.34	0.03
Synperonic PE/L-61	0.167	0.006

**Table 3**

Flow properties of liquisolid powder mixtures.

Formulations	Cf%	Position
PEG200 20%w/w, R10	22.22	Passable
PEG200 20%w/w, R20	23.64	Passable
PEG200 40%w/w, R10	29.03	Poor
PEG200 40%w/w, R20	39.29	Very poor
Conventional	17.39	Good
Synperonic 20%w/w, R10	24.11	Passable
Synperonic 20%w/w, R20	21.21	Passable
Synperonic 40%w/w, R10	31.03	Poor
Synperonic 40%w/w, R20	35.38	poor

strong as PEG200 formulations in case of conventional formulations or in Synperonic PE/L-61 formulations when the vehicle presents in less percentages. This could lead to suggest a probability of intermolecular hydrogen bonding formation between the drug and the liquid vehicle.

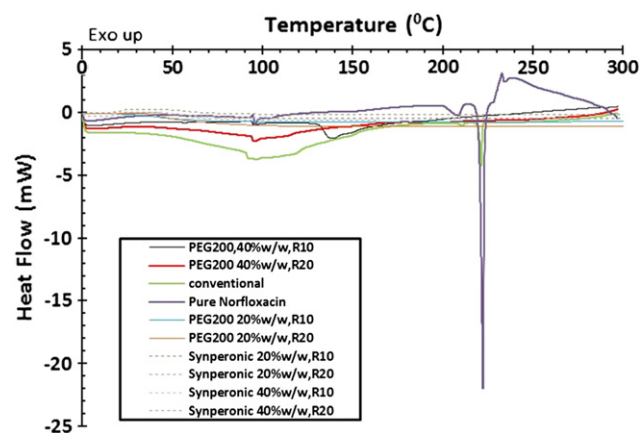
Supporting the presence of hydrogen bonds is the disappearance of sharp vibrations between 1650  $\text{cm}^{-1}$  and 1550  $\text{cm}^{-1}$  in all liquisolid formulations (PEG200 and Synperonic PE/L-61) compared with pure norfloxacin. This region denotes the bending vibration of the secondary amine functional group ( $\text{R}_2\text{NH}$ ). This indicates that there is hydrogen bond between N–H functional group in norfloxacin and the hydrogen molecule in hydroxyl group in the vehicle. Consequently, the formation of hydrogen bonds between the drug and the vehicle contributes in increasing the solubility of the drug in the vehicle, which reflects mainly on the dissolution profiles [10].

As a result, FTIR spectra analysis complies with DSC results, indicating a solubilisation of norfloxacin crystals in liquid vehicles, decreasing the crystallinity of norfloxacin.

### 3.3. Evaluation of norfloxacin liquisolid tablets

#### 3.3.1. Drug content uniformity, tablet dimensions, hardness, tensile strength, friability and disintegration tests

A summary of results expressed by the average and the standard deviations of tablet hardness, tensile strengths, friability, disintegration and drug content for all liquisolid (PEG200 and Synperonic PE/L-61) and conventional tablets is presented in Table 4. British Pharmacopeia specifies the accepted limits of the percentage of the active ingredient in tablets between 85% and 115% [9]. According to this, all liquisolid (PEG200 and Synperonic PE/L-61) and conventional formulations are



**Fig. 3.** Differential scanning calorimetry for norfloxacin pure powder, conventional and all liquisolid formulations.



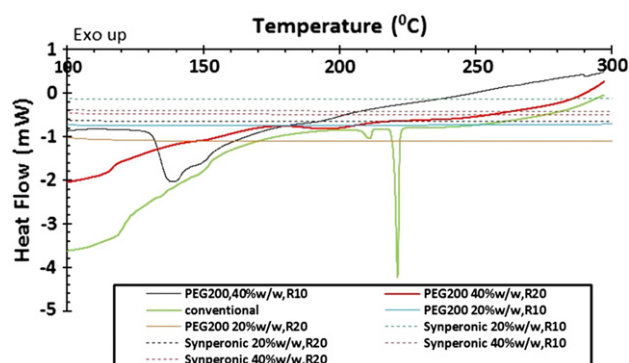


Fig. 4. Differential scanning calorimetry for conventional and all liquisolid formulations without pure norfloxacin powder.

in this range (Table 4). Moreover, the statistical analysis for the drug contents indicated that there is no significant differences between either conventional and PEG200 formulations ( $P = 0.430$ ), conventional and Synperonic PE/L-61 formulations ( $P = 0.293$ ) or PEG200 and Synperonic PE/L-61 formulations ( $P = 0.293$ ). The reason of this could be referred to the high percentage of the carrier excipient in the unit dose of the PEG200 tablets (ranged between 71.2% and 74.6%), the Synperonic PE/L-61 tablets (from 75.83% to 78.41%) and the conventional tablet (79.73%). This leads to increase in the surface area that absorbs the liquid medication into the internal part of the carrier framework, allowing a homogeneous distribution throughout the bed powder of the batches [16]. As a result of this, all drug percentages are ranged between over 90% and less 105%.

The reason for variations in the tablet thickness can be explained in terms of the variation in the weights of the tablets, which are determined to allow sufficient tablet hardness with an appropriate disintegration time (usually less than 5 min).

The tensile strength of the Synperonic PE/L-61 formulations show more consistency (i.e. less variations) compared with the PEG200 formulations. This is expressed by F-test which determines a significant difference between The Synperonic PE/L-61 and PEG200 formulations ( $P = 0.011 < 0.05$ ). This is probably due to the fact that Synperonic PE/L-61 formulations were prepared using compatible liquisolid test which allows preparing the formulations at a plateau compression forces with an optimum pactisity value (20 kg/g). As a result of this, it determines lesser tensile strengths compared with the PEG200 formulations, which were prepared depending on the acceptable flowability value for both carrier and coating materials by angle of slide test, not allowing a sufficient control in the compression forces.

From industrial perspective, it is important to balance between disintegration time and tablet hardness. Moreover, there is a relationship between tablet hardness and its porosity. Decreasing the porosity among the particles in the tablets is due to increasing the compression forces and the hardness of the tablets. Consequently, there is a decrease in the intermolecular distance, promoting more formation of solid bridges among the tablet particles [11].

In this study, the range of hardness is between 45.60 N and 91.94 N (Table 4).

Using microcrystalline cellulose (Avecel PH101) as a carrier with high percentages leads to close the surface and increase hydrogen bonding between the molecules. This is due to the ability of the carrier to exhibit plasticity which explains the deformation of particles undergoing non-reversible changes of shape as a response to applied compression forces [18].

The investigation of the percentages of weight loss in friability tests demonstrates that the all formulations passed the BP specifications [9]. In other words, no formulations lost more than 1% from tablet weights,

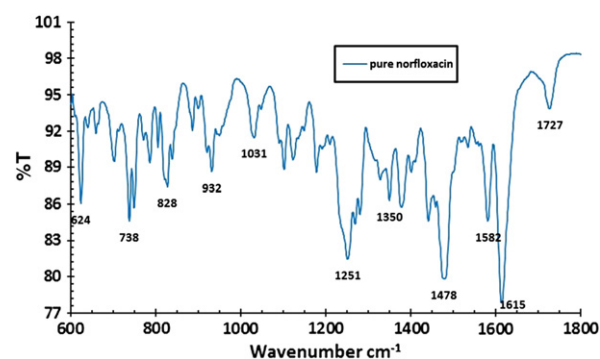


Fig. 5. FTIR spectrum of pure norfloxacin powder.

with no markedly cracked or broken tablets during the test. Consequently, liquisolid tablets have the ability to resist the expected abrasions when applying further manufacturing processes.

For disintegration data, the averages of the time of the PEG200 formulations is over 90 s, whereas the average of the Synperonic PE/L-61 formulations records a time less than 50 s. Table 4 presents the range of the time of the PEG200 formulations between 91.6 and 275.6 s, while the time of the Synperonic PE/L-61 formulations is between 30.3 and 62.5 s. Because of less variations in the case of the Synperonic PE/L-61 liquisolid formulations compared with the PEG200 liquisolid formulations, the statistical analysis showed no significant differences between the PEG200 and the conventional formulations ( $P = 0.06 > 0.05$ ), whereas there is a significant difference ( $P = 0.01 < 0.05$ ) in the case of the comparison between the time of disintegration of the Synperonic PE/L-61 and the conventional tablets. To sum up, all liquisolid formulations recorded disintegration times less than 5 min, although the PEG200 formulations recorded longer time than the Synperonic PE/L-61 formulations. Nevertheless, all of them meet the BP specifications, which are less than 15 min in the case of uncoated tablets [9]. Seeing rapid disintegration times through improving tablet dissolution profiles is important due to the fast division that is provided into surface fragments, reaching to higher surface areas for dissolution processes. Mentioning this would drive toward specifying the reasons of the fast disintegration, which relates to presenting both microcrystalline cellulose and carmellose sodium in high percentages in the tablet dosage forms. In the same direction, PEG200 demonstrated slightly longer disintegration time, which can be referred to the lower percentages of microcrystalline cellulose in the formulations. In summary, the type of liquid vehicles, the percentage of the

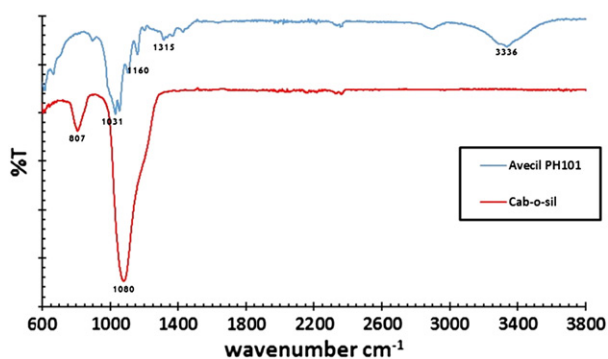


Fig. 6. FTIR spectra for pure excipients (Avecel PH101 and Cab-o-sil M5DP).

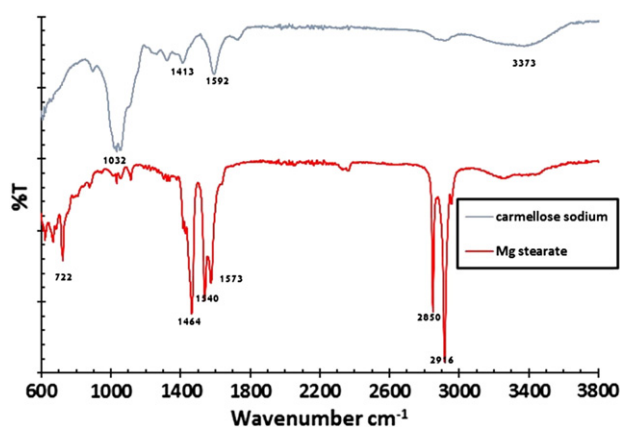


Fig. 7. FTIR spectra for pure excipients (carmellose sodium and magnesium stearate).

carrier and the percentage of the disintegrants said to be the main factors controlling the time of the liquisolid tablet disintegration.

### 3.3.2. In vitro dissolution

It is clear that the percentage of norfloxacin release in the acetate buffer dissolution medium is significantly higher than in the distilled water dissolution medium ( $f_2 < 26\%$  for all comparisons between each liquisolid and conventional formulations in the two dissolution media). The percentage of the drug release was over 85% in all liquisolid and conventional tablets after 90 min, whereas it was no more than 63% in distilled water dissolution medium.

Fig. 11 shows all PEG200 liquisolid tablets with conventional tablets in distilled water. In this profile, the conventional tablet shows the highest percentage of drug release compared with the other liquisolid tablets. However, at the first 20 min, tablets with 40% w/w norfloxacin: PEG200 liquid medication with the both excipient ratios ( $R = 10$  and  $20$ ) record higher percentage of norfloxacin release compared with the conventional one. Then, the conventional dissolution profile continues raising over both liquisolid tablets. On the other hand, when the percentage of norfloxacin: PEG200 liquid medication decreases, the dissolution profiles decrease significantly ( $f_2 < 35\%$  when comparing the PEG200 formulations 20%w/w and 40%w/w in distilled water), reaching to only 30% after 90 min. In Fig. 12, all PEG200 liquisolid and conventional tablets record similar dissolution profiles with over 85% drug release in the first 30 min.

In the case of Synperonic EP/L-61 dissolution profiles (Figs. 13 and 14), the drug release from conventional tablets is still higher than

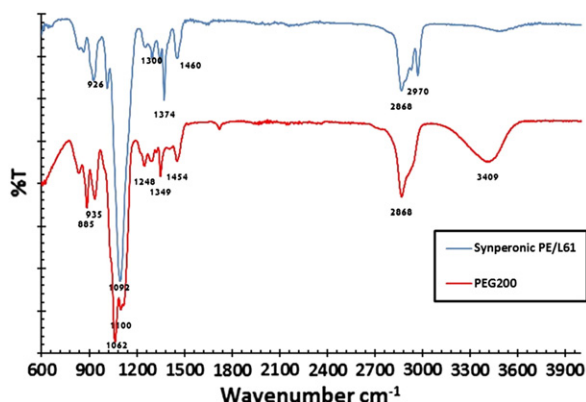


Fig. 8. FTIR spectra for liquid vehicles (PEG200 and Synperonic PE/L-61).

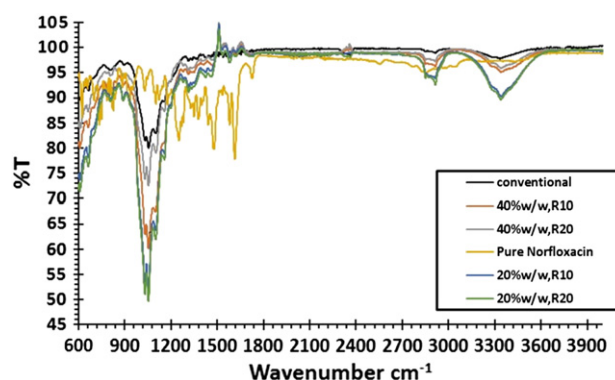


Fig. 9. FTIR spectra for pure norfloxacin, conventional powder, and the all PEG200 liquisolid formulations.

most of the Synperonic PE/L-61 liquisolid tablets, except a slightly increase in one dissolution profile, which drug: liquid medication percentage is at 40%w/w and the excipient ratio equals to 10, nevertheless it is not a significant increase in the drug release ( $f_2 = 61.41\%$ ). The liquisolid tablet (20%w/w,  $R = 20$ ) shows a significant decrease in comparison with the conventional tablet ( $f_2 = 44.7\%$ ). In general, all Synperonic PE/L-61 profiles keep the same order of the PEG200 dissolution profiles, when comparing the liquisolid with the conventional tablets in both dissolution media (Figs. 13 and 14).

Finally, the comparison between the dissolution profiles of the Synperonic PE/L-61 liquisolid tablets and the PEG200 liquisolid tablets having the same composition determine that there is no significant differences in all formulations, except the tablets having drug: liquid medication percentage equals to 20%w/w and  $R = 10$ , where the Synperonic PE/L-61 tablet has a significantly higher norfloxacin release ( $f_2 = 44.04\%$  in distilled water and 40.98% in acetate buffer).

From dissolution profiles, many points can be concluded. First of all, the enhancement of norfloxacin in two liquisolid formulations (40%w/w norfloxacin: PEG200 liquid medication,  $R = 10$  and  $R = 20$ ) compared with the conventional tablets in distilled water dissolution medium can probably be explained by Noyes–Whitney equation:  $\frac{dc}{dt} = \frac{DS(C_s - C)}{h}$  where  $dc/dt$  is the dissolution rate of the drug particles,  $S$  is the surface area of the interface between the dissolving substance and the solvent,  $D$  is the diffusion coefficient,  $h$  is the thickness of the boundary layer of the solvent at the surface of the dissolving substance,  $C_s$  is the mass

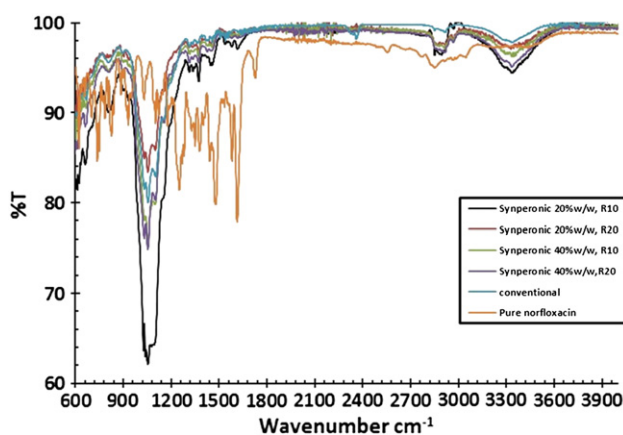


Fig. 10. FTIR spectra for pure norfloxacin, conventional powder, and the all Synperonic PE/L-61 liquisolid formulations.

**Table 4**Tablet hardness, tensile strengths, disintegration time, friability and content uniformity for conventional and the all liquisolid tablets (average  $\pm$  standard deviation).

Formulations	Hardness (N)	T-strength (MPa)	Disintegration (seconds)	Friability %	Content uniformity %
PEG200 20%w/w,R10	51.97 $\pm$ 3.75	0.880 $\pm$ 0.189	275.6 $\pm$ 61.5	0.474	94.83 $\pm$ 1.6
PEG200 20%w/w,R20	91.93 $\pm$ 21.5	1.508 $\pm$ 0.368	192.8 $\pm$ 70	0.405	104.73 $\pm$ 5.1
PEG200 40%w/w, R10	66.93 $\pm$ 42.5	1.123 $\pm$ 0.697	148.2 $\pm$ 72.8	0.842	94.90 $\pm$ 3.1
PEG200 40%w/w, R20	45.60 $\pm$ 7.18	0.707 $\pm$ 0.085	91.7 $\pm$ 11.4	0.724	96.74 $\pm$ 7.5
Conventional	47.56 $\pm$ 5.63	0.754 $\pm$ 0.119	62.5 $\pm$ 9.5	0.864	99.94 $\pm$ 0.52
Synperonic 20%w/w,R10	46.85 $\pm$ 3.01	1.172 $\pm$ 0.083	49.2 $\pm$ 6.9	0.304	98.62 $\pm$ 5.6
Synperonic 20%w/w, R20	57.75 $\pm$ 3.58	1.097 $\pm$ 0.067	39.8 $\pm$ 11.3	0.275	100.91 $\pm$ 5.1
Synperonic 40%w/w, R10	48.27 $\pm$ 2.9	1.206 $\pm$ 0.064	40.3 $\pm$ 4.4	0.167	100.49 $\pm$ 1.7
Synperonic 40%w/w, R20	58.25 $\pm$ 2.4	1.059 $\pm$ 0.043	30.3 $\pm$ 1.5	0.338	102.90 $\pm$ 2.3

concentration of the substance on the surface and  $C$  is the mass concentration of the substance in the bulk of the solvent.

From this equation, only two factors could affect the enhancement of the drug release, which are the drug concentration gradient in the diffusion layer ( $C_s - C$ ) and the surface area of the interface between the dissolving substance and the solvent ( $S$ ). This is due to the speed of the paddle that is constant (50 rpm) and the dissolution medium (distilled water) that is the same for all the comparative tablet dissolution profiles. As a result, the thickness of the boundary layer ( $h$ ) and the diffusion coefficient ( $D$ ) are not included in this situation.

Regarding the surface area of the interface ( $S$ ), it is directly proportional to the dissolution rate of the drug. Consequently, the drug dissolves in a water miscible liquid vehicle in the liquisolid tablets, which has good wettability. This enhances the wetting characterization of norfloxacin particles, increasing the surface area of the interface between the liquid medication and the dissolution medium compared with the surface area of the drug particles alone and the dissolution medium in the case of the conventional tablets, which leads to the increasing in the rate of norfloxacin release [19,20].

The second reason relates to the saturation solubility ( $C_s$ ). At micro-environment, there is a high possibility that an infinite amount of liquid-vehicle is to diffuse away with norfloxacin molecule from liquisolid particles, since the liquid vehicle works as co-solvent in order to improve the solubility of the drug, leading to increase the concentration gradient and the percentage of the drug release [7]. The third reason is the solubility of norfloxacin in PEG200, which is higher than the solubility of the drug in either Synperonic EP/L-61 or distilled water. Thus, a certain amount of PEG200 added to liquisolid tablets would increase the dissolution rate of the drug [11].

To sum up, three main factors are able to participate in enhancing the two PEG200 liquisolid formulations over the conventional in distilled water; the increase in the surface area of the interface between

the dissolving liquid medication and distilled water, the increase of the saturation concentration at molecular level and the higher solubility of norfloxacin in PEG200 surfactant compared with the solubility in distilled water and Synperonic PE/L-61 co-polymer.

An interesting point that can be noticed from dissolution profiles is that the percentage of drug release of the conventional tablets is higher than most liquisolid tablets. This could be referred to the nature of norfloxacin solid particles. This drug has a unique solid structure that allows the pharmaceutical hydrate to be more water soluble from anhydrous forms.

In general, existence of water molecule in solid state of drugs can decrease the solubility of the drug because water molecule works to increase the thermodynamic stabilization of the solid structure by the interaction of water molecules. However, norfloxacin is exceptional to this rule. This is due to that the hydrate formation of norfloxacin can occur in the anhydrous state. In addition, the hydration can change the interaction between norfloxacin molecules from hydrogen bonding to ionic bonding by proton transfer process from COOH group to NH group in the solid state. In other words, water molecules convert the drug from neutral state to zwitterionic state which increases the percentage of ionization of the drug and the percentage of dissolution rate. Therefore, the tablet dissolution behaviour was adversely affected by lower humidity [21]. As a result, these phenomena can explain the improvement of the conventional tablet dissolution profile over liquisolid tablet profiles because the drug particles in the conventional tablet are more exposed to water molecules compared to liquisolid tablets.

To support this conclusion, dissolution tests were applied on liquid medications consisting of either norfloxacin: PEG200 or norfloxacin: Synperonic EP/L-61 alone without adding powder excipients. The same concentrations of drug in the solvent that was used to prepare liquisolid formulation were used in these tests. Also, the same dissolution

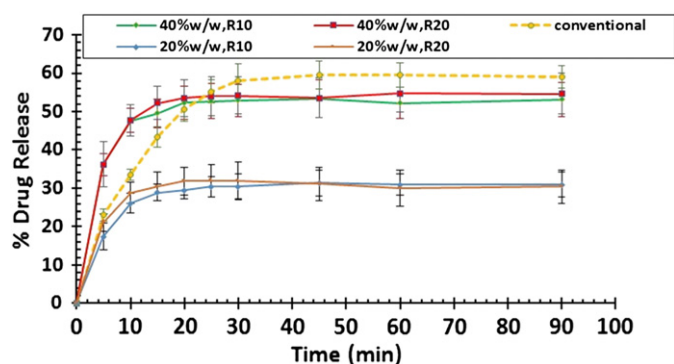


Fig. 11. Percentage drug released from PEG200 liquisolid and conventional tablets in distilled water.

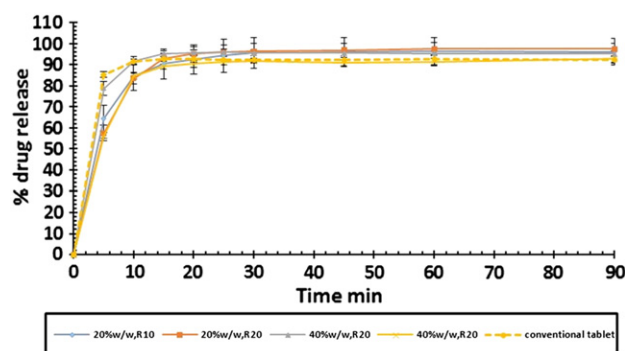


Fig. 12. Percentage drug released from PEG200 liquisolid and conventional tablets in acetate buffer (pH = 4) dissolution medium.



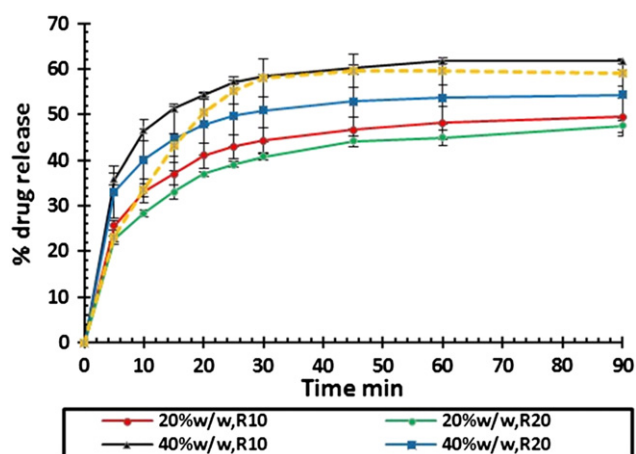


Fig. 13. Percentage drug released from Synperonic PE/L-61 liquisolid and conventional tablets in distilled water dissolution medium.

conditions were applied, i.e. 750 ml distilled water maintained at 37 °C with a paddle speed 50 rpm. The samples were measured at 15 and 30 min and the differences between the percentages of the drug release at the withdrawn time were calculated. All the results were summarised in Table 5 and supported with images (Fig. 15) taken after 30 min of the dissolution test starts.

Table 5 and Fig. 15 show clearly that there is a strong interaction between norfloxacin particles and PEG200, preventing water molecules to enter the solid framework of the drug particles, and making the percentage of norfloxacin release in dissolution medium from liquid medication is less than conventional one. This interfering layer is not seen in case of Synperonic PE/L-61 liquid medication (40%w/w) and a fragile layer seen at concentration (20% w/w). As a result, the increase volume of liquid vehicle, PEG 200, leads to decrease the percentage of norfloxacin release as the constituted interfering layer prevent water molecules to enter the liquid medication and induces the drug molecules to form ionic bonds. Instead of this, the hydrogen bonds are formed between the norfloxacin molecules themselves and the PEG200 and to some extent with Synperonic PE/L-61.

Moreover, all liquisolid and conventional tablets show a percentage of drug release less than 65% in distilled water. The reason of this in addition to the low percentage of norfloxacin ionization in distilled water is that the drug particles could precipitate inside the cavities of the porous carrier on contact with liquid medication with the release medium [22]. As a consequence of this, the drug release would retain.

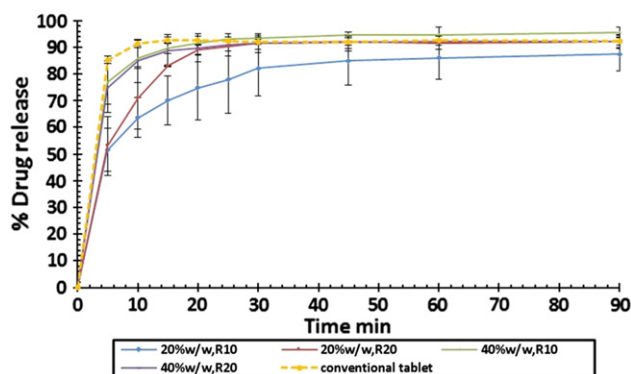


Fig. 14. Percentage drug released from Synperonic PE/L-61 liquisolid and conventional tablets in acetate buffer (pH = 4) dissolution medium.

This can be noticed when the increase of the excipient ratio ( $R = 20$ ). The higher percentage of Avicel PH101, the lower percentage of the drug released in the dissolution medium. To overcome this problem, poly vinyl pyrrolidone (PVP) can be used as a crystallization inhibitor. Furthermore, PVP can also work as binder during compaction, which leads to an increase of the liquid load factor [22].

Finally, these factors affecting the percentage of drug release (e.g. Figs. 11 and 12) may enhance the oral bioavailability of these formulations. For example, a solid dispersion formulation prepared at ratio (20:80) norfloxacin: PEG6000 presents better relative bioavailability percentage (67%) when it is compared with powder of pure norfloxacin (49%) [23]. In the same study, which was carried out on male albinos' rabbits, the solid dispersion formulation showed maximum plasma concentration closer to the plasma concentration of norfloxacin acetic acid solution (pH = 4.5), which was recorded as 100% relative bioavailability [23], led to conclude that in our study, the liquisolid formulations of norfloxacin prepared with PEG200 are expected to enhance the drug oral bioavailability. Additionally, it is reported that aqueous solubility and the in-vitro dissolution profile are not the unique explanation of the behaviour of the oral bioavailability of norfloxacin, although they help in indicating the physicochemical properties of the drug [23].

### 3.3.3. Kinetic model analysis of drug release

Table 6 presents the values of the squared correlation coefficients for liquisolid and conventional tablets, using zero order, first order, Higuchi and Hixson–Crowell kinetic release models. Broader reporting, the highest  $R^2$  values were recorded when applying Higuchi or Hixson–Crowell models for all types of tablets. Moreover, all liquisolid tablets containing Synperonic PE/L-61 have higher  $R^2$  values form those including PEG200. In addition to this, the data which is considered to build the models are between 5 and 15 min, whereas the rest points (i.e. from 20 to 90 min) are excluded as the dissolution profiles reached to the steady state where the drug release gives a straight parallel line to the time axis. Paired  $t$ -test shows a slightly significant difference between  $R^2$  values of both Hixson–Crowell and Higuchi models ( $P = 0.051 < 0.1$ ), where Hixson–Crowell recorded a slightly higher accuracy than Higuchi model. This situation is applied on all types of tablets, where all of them recorded  $R^2$  values higher than 0.990.

Regarding Higuchi model, Fick's law consists of a fundamental diffusion background on which the release of norfloxacin into dissolution medium depends. This law states that a driving forces coming from a concentration gradient between the tablet and the bulk solution diffuses the drug particles from tablet toward the dissolution medium [14]. As a consequence of this hypothesis, the dispersion of norfloxacin molecules in the liquid vehicles (PEG200 or Synperonic PE/L-61) would affect the increasing of the saturation solubility ( $C_s$ ) and the relative concentration gradient ( $C_s - C$ ) at different grades, allowing dissolving of the drug particles in the dissolution medium [11].

On the contrary, Hixson–Crowell release model does not take Fick's law in its assumptions. In other words, the diffusion of the drug particles from the tablet is not included here. Hixson–Crowell model states that there is a same effect of liquid agitation on all parts of the surface, and there is no need to assume any particular shape of the drug crystal because the model considers all of them to have a spherical shape through the solution. Consequently, differences in the dissolution rate from different faces of the tablet are negligible, and the main effects of controlling the speed of the particle transformation are limited only to the proportional change of the surface with the time and the agitation. Therefore, the persistency of the drug particles to change its shape assumption as a cubic root relationship with the time gives the quantitative verification to the release model [15]. To some extent, the squared correlation coefficient values translate this assumption by dividing the tablets into two main groups; the first one includes all PEG200 liquisolid tablets which are less accurate, and the second includes the Synperonic PE/L-61 liquisolid and conventional tablets which are more accurate. As a result, the solubility of the drug in the liquid

**Table 5**

The percentage of drug release from the dissolution tests without powder excipients and the difference between them at 15 and 30 min.

Liquid vehicle	20%w/w (drug: liquid medication)					40%w/w (drug: liquid medication)				
	abs <sup>a</sup>	%R <sup>b</sup>	abs	%R	Difference <sup>c</sup>	abs	%R	abs	%R	Difference
PEG200	15 min	15 min	30 min	30 min		15 min	15 min	30 min	30 min	
	0.352	33.531	0.410	39.056	5.525	0.407	38.770	0.454	43.247	4.477
	0.431	41.056	0.495	47.153	6.097	0.457	43.533	0.570	54.297	10.764
	0.346	32.959	0.445	42.390	9.431	0.509	48.487	0.600	57.155	8.669
				Average = 7.017						7.970
Synperonic PE/L-61				ST DEV <sup>d</sup> = 2.109						3.201
	0.590	56.203	0.741	70.587	14.384	0.467	44.486	0.757	72.111	27.625
	0.379	36.103	0.575	54.774	18.671	0.586	55.822	0.832	79.255	23.434
	0.538	51.249	0.800	76.207	24.958	0.470	44.772	0.730	69.539	24.767
				Average = 19.338						25.275
				ST DEV = 5.318						2.141

<sup>a</sup> abs: absorbance at 321 nm wavelength.<sup>b</sup> %R: percentage of norfloxacin release in distilled water.<sup>c</sup> Difference: differences between the %R at 15 and 30 min.<sup>d</sup> ST DEV: standard deviation of the difference.

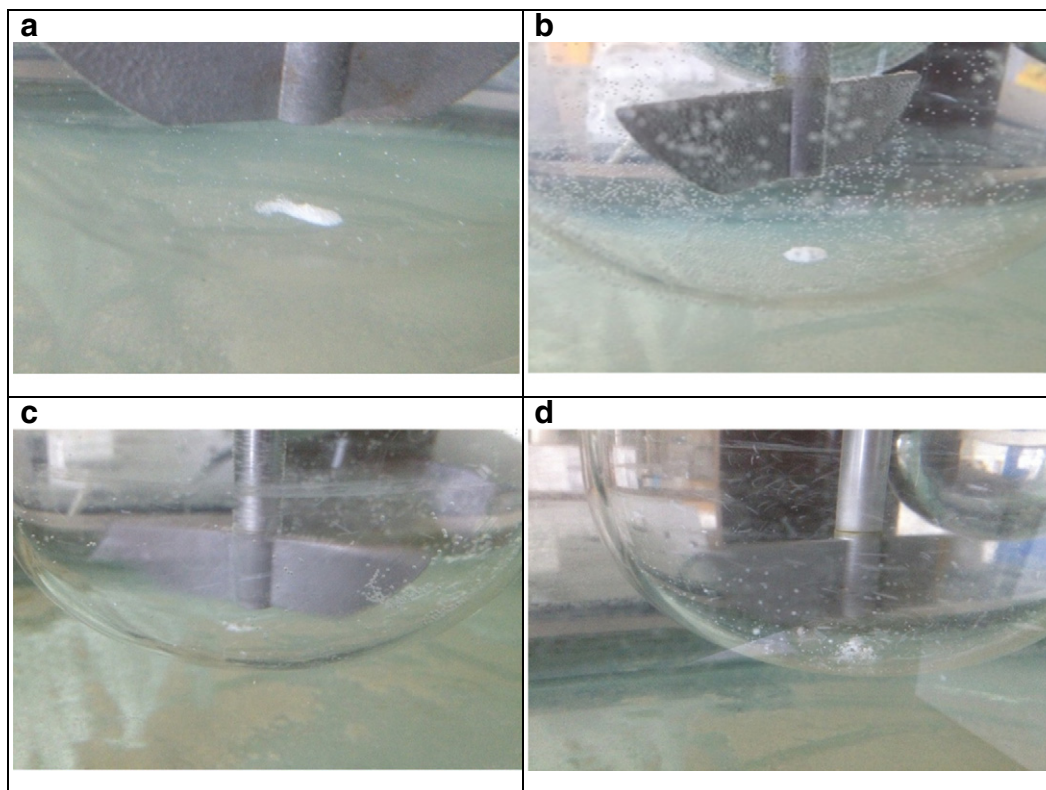
vehicle may have an effect in determining the changing of the crystal shape during the dissolution test. Paired *t*-test signifies the difference in the accuracy of the Hixson–Crowell model when compared with the Higuchi model ( $P = 0.051 < 0.1$ ). This gives a further support to the Hixson–Crowell's assumption and explanations.

#### 4. Conclusion

Norfloxacin releasing from lquisolid tablets is not necessarily faster than conventional counterpart tablet. The chemical structure of the hydrophobic drug and its interaction with the liquid vehicle determine

to large extent the dissolution behaviour of the drug. Furthermore, this research represents that the solubility of the drug in the liquid vehicle is not necessarily considered as a main effect in lquisolid dissolution process.

On the other hand, using compatibility lquisolid test to indicate the optimum load factor in the case of Synperonic PE/L-61 lquisolid formulations provide more consistent qualified tablets compared with PEG200 lquisolid tablets, which was prepared depending on determining the flowability of liquid load potential of Avicel PH101 and Cab-O-Sil M5DP using angle of slide test, although the weight of the unit dose is lesser in the case of the PEG200 lquisolid formulations. Moreover,



**Fig. 15.** (a) Norfloxacin: PEG200 liquid medication (20%/w/w) after 30 min in the mock dissolution test. (b) Norfloxacin: PEG200 liquid medication (40%/w/w) after 30 min in the mock dissolution test. (c) Norfloxacin: Synperonic PE/L-61 liquid medication (40%/w/w) after 30 min in the mock dissolution test. (d) Norfloxacin: Synperonic PE/L-61 liquid medication (20%/w/w) after 30 min in the mock dissolution test.



**Table 6**

Release parameters of norfloxacin liquisolid formulations.

Tablets/models	Zero order	First order	Higuchi	Hixson–Crowell
20%w/w drug/PEG200, R10	0.919	0.927	0.955	0.959
20%w/w drug/PEG200, R20	0.879	0.886	0.924	0.927
40%w/w drug/PEG200, R10	0.853	0.864	0.902	0.908
40%w/w drug/PEG200, R20	0.939	0.954	0.969	0.977
Conventional	0.999	0.999	0.996	0.992
20%w/w drug/Synperonic, R10	0.964	0.972	0.987	0.990
20%w/w drug/Synperonic, R20	0.998	0.999	0.999	0.998
40%w/w drug/Synperonic, R10	0.955	0.968	0.981	0.987
40%w/w drug/Synperonic, R20	0.985	0.990	0.998	0.999

both DSC thermograms and the vibrational spectra of FTIR reflected the state of the crystallinity of the norfloxacin, which disappeared in liquisolid formulations, and the possibility of hydrogen bond formation with liquid vehicle, respectively. Finally, this paper suggests making further studies on using PVP in liquisolid formulations due to its ability to work as a crystallizing inhibitor, which probably increases the percentage of norfloxacin release in distilled water as a dissolution medium.

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